



بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

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Evaluation of Vitamin (A) Deficiency among Critically Ill Children with Sepsis

Thesis

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قالوا

سببنا انك لا تعلم لنا
إلا ما علمتنا إنك أنت
العليم العظيم

صدق الله العظيم

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List of Abbreviations

Abb.	Full term
<i>AIDS</i>	<i>Acquired Immune Deficiency Syndrome</i>
<i>AP-1</i>	<i>Adaptor protein 1</i>
<i>APC</i>	<i>Activated protein C</i>
<i>ACTH</i>	<i>Adrenocorticotrophic hormone</i>
<i>ATRA</i>	<i>All-trans-retinoid acid</i>
<i>AMPs</i>	<i>Antimicrobial peptides</i>
<i>ARDS</i>	<i>Acute respiratory distress syndrome</i>
<i>AUC</i>	<i>Area under curve</i>
<i>BMI</i>	<i>Body mass index</i>
<i>BPS</i>	<i>Best practice statements</i>
<i>CAP</i>	<i>Cholinergic anti-inflammatory pathway</i>
<i>CRBP II</i>	<i>Cellular retinol binding protein II</i>
<i>CI</i>	<i>Confidence interval</i>
<i>CRH</i>	<i>Corticotrophin releasing hormone</i>
<i>CRT</i>	<i>Capillary refilling time</i>
<i>DCs</i>	<i>Dendritic cells</i>
<i>DIC</i>	<i>Disseminated intravascular coagulation</i>
<i>DNA</i>	<i>Deoxyribonucleic acid</i>
<i>ED</i>	<i>Emergency department</i>
<i>EGDT</i>	<i>Early goal-directed therapy</i>
<i>ELISA</i>	<i>Enzyme-linked immunosorbent assay</i>
<i>ERK1/2</i>	<i>Extracellular signal-regulated kinase 1/2</i>
<i>FAO</i>	<i>Food and agriculture organization</i>
<i>FFQ</i>	<i>Food frequency questionnaire</i>
<i>FiO₂</i>	<i>Inspired oxygen fraction</i>
<i>GRV</i>	<i>Gastric residual volumes</i>
<i>GM-CSF</i>	<i>Granulocyte-macrophage colony-stimulating factor</i>
<i>HPA</i>	<i>Hypothalamic–pituitary–adrenal</i>

List of Abbreviations (Cont....)

Abb.	Full term
<i>IBM SPSS</i>	<i>Statistical Package for Social Science</i>
<i>ICU</i>	<i>Intensive care unit</i>
<i>iNO</i>	<i>inhaled nitric oxide</i>
<i>IFN</i>	<i>Interferon</i>
<i>INF-γ</i>	<i>Interferon gamma</i>
<i>IRF7</i>	<i>Interferon regulatory factor 7</i>
<i>IL</i>	<i>Interleukin</i>
<i>IL-6</i>	<i>Interleukin-6</i>
<i>INR</i>	<i>INTERNATIONAL normalized ratio</i>
<i>IQR</i>	<i>Inter-quartile range</i>
<i>IO</i>	<i>Intraosseous</i>
<i>IOM</i>	<i>Institute of Medicine</i>
<i>IRAK-M</i>	<i>Interleukin-1 receptor-associated kinase-M</i>
<i>IRF3</i>	<i>Interferon regulatory factor 3</i>
<i>IV</i>	<i>Intravenous</i>
<i>IVIG</i>	<i>Intravenous immunoglobulin</i>
<i>JAMA</i>	<i>Journal of American Medical Association</i>
<i>JNK</i>	<i>C-Jun N-terminal kinase</i>
<i>LPS</i>	<i>Lipopolysaccharide</i>
<i>MAC</i>	<i>Mid arm circumference</i>
<i>MAP</i>	<i>Mean arterial pressure</i>
<i>NFHS-3</i>	<i>National Family Health Survey-3</i>
<i>NFκB</i>	<i>Nuclear factor kappa B</i>
<i>NF-κB</i>	<i>Nuclear factor-κB</i>
<i>NK</i>	<i>Natural killer</i>
<i>NO</i>	<i>Nitric oxide</i>
<i>NPC2</i>	<i>Niemann–Pick C2 protein</i>
<i>NPV</i>	<i>Negative predictive value</i>

List of Abbreviations (cont....)

Abb.	Full term
OR.....	Odds ratio
PALS	Pediatric advanced life support
PAMPs.....	Pathogen associated molecular patterns
PaO2.....	Arterial oxygen partial pressure
PEEP	Positive end-expiratory pressure
PICUs	Pediatric intensive care units
PO2.....	Partial pressure of oxygen
PPV.....	Positive predictive value
PRRs.....	pattern recognition receptors
pSOFA	Pediatric SOFA
qSOFA.....	Quick SOFA
RA.....	Retinoic acid
RAE	Retinol activity equivalent
RAR	Retinoic acid receptor
RBP.....	Retinol-binding protein
RDA	Recommended Dietary Allowance
RE.....	Retinol equivalent
RNS	Reactive nitrogen species
ROC	Receiver operating characteristic curve
ROS	Reactive oxygen species
RXR	Retinoid X receptor
SSC.....	Surviving sepsis campaign
ScvO2.....	Central venous oxygenation saturation
SIGIRR.....	Single Ig IL-1R-related molecule.
SIRS	Systemic inflammatory response syndrome
SOCS1.....	Suppressor of cytokine signaling 1
SOFA.....	Sequential Organ Failure Assessment
ST2	Stimulation expressed gene 2

List of Abbreviations (Cont....)

Abb.	Full term
<i>TAMOF</i>	<i>Thrombocytopenia associated multiple organ failure</i>
<i>Th17</i>	<i>T helper 17</i>
<i>TIR</i>	<i>Toll Interleukin-1 Receptors</i>
<i>TLRs</i>	<i>Toll-like receptors</i>
<i>TNF</i>	<i>Tumor necrosis factor</i>
<i>TNF-α</i>	<i>Tumor necrosis factor-α</i>
<i>TOLLIP</i>	<i>Toll interacting protein</i>
<i>VA</i>	<i>Vitamin A</i>
<i>VAD</i>	<i>Vitamin A deficiency</i>
<i>VAS</i>	<i>Vitamin A supplementation</i>
<i>VADDs</i>	<i>Vitamin A deficiency disorders</i>
<i>WHO</i>	<i>WORLD Health Organization</i>

Evaluation of Vitamin (A) Deficiency among Critically Ill Children with Sepsis

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Abstract

Background: Vitamin A is an immunomodulatory, and its deficiency may cause impaired immune function, which are found in sepsis. There is a biological rationale that vitamin A deficiency (VAD) may be a contributing factor related to poor clinical outcomes in patients with sepsis.

Aim of the Work: to assess the prevalence of vitamin A deficiency in critically ill children with sepsis and its association with clinical outcomes.

Patients and Methods: This cross-sectional study included 40 critically ill children with sepsis who were admitted to the paediatric intensive care unit. The control group consisted of 40 age- and sex-matched approximate-health children from outpatient clinic. For the measurement of serum vitamin A status, blood samples were taken from all patients within the first 24 hours of admission. The vitamin A status of the sepsis and control groups were compared. Univariate and multivariate approaches were used to assess the link between vitamin A deficiency and sepsis.

Results: The study enrolled 40 children with sepsis and 40 matched healthy children so there was no statistically significant difference between controls and patients among age and sex, with median age 4 (2 – 12) months for both groups with male predominance (60.0%). Regarding body measures there was a high statistically significant lower values among patients group than controls group for z score of weight, height/length, body mass index (BMI) and mid arm circumference (MAC) of the studied subjects, that indicated increased malnutrition prevalence among septic children than control group. In the present study, by comparing VAD between patients and controls, there was high statistically significant difference as all septic patients (100%) had VAD and the VAD among healthy control was found in 30% of them. We also found that patients with septic shock, patients who were nothing per os (NPO), patients on ventilators and died patients were more deficient in vitamin A level than other patients compared with them (high statistically significant difference), illustrated that VAD may be had a role in sepsis related morbidity and mortality. There was a positive correlation between vitamin A and BMI z score and MAC while there was a negative correlation with prism 3 and prism 4. ROC curve for assessment of vitamin A as a predictor of sepsis, found that at cut off value $\leq 9 \mu\text{g/dl}$, the Sensitivity, Specificity, positive predictive value (PPV) and negative predictive value (NPV) were 100% for each.

Conclusion: low level of vitamin A, lower than or equal to $9 \mu\text{g/dl}$ was associated with sepsis, septic shock, and higher PRISM score. Vitamin A deficiency may be a marker of morbidity and mortality in critically ill children with sepsis.

Key words: Sepsis, Vitamin A, vitamin A deficiency.

INTRODUCTION

Sepsis is a condition in which the immune system over-reacts to infection, releasing inflammatory mediators into the peripheral blood and triggering widespread inflammation. It is considered as a worldwide health problem, resulting in millions of deaths each year. The mortality of severe sepsis was reported to be as high as 34.6% in children (*Wang et al., 2014*). It has been revealed that over 50% of deaths in preschool children were due to severe infectious diseases that could result in sepsis (*Liu et al., 2012*).

Sepsis and septic shock are among the most important medical emergencies throughout the world. Advancement in the life support technologies have proven to be insufficient in reducing the mortality and morbidity arising from severe sepsis. In the era of multi-drug resistance, it becomes imperative that such cases should be diagnosed at the earliest and appropriate treatment and management measures should be initiated for better patient outcome/care (*Ramana et al., 2014*).

Sepsis is, worldwide, one of the leading causes of death among infants and children (*Hermon et al., 2020*). A steady increase in the incidence of severe sepsis has been reported in the past decades (*Hartman et al., 2013*). As a public health problem, sepsis has posed a significant burden on extensive health care resources for many years. It is reported as a complicated immune disorder characterized by both a hyper